



# DRUG THERAPY AND PREGNANCY: UNKNOWN RISKS LEAD TO HARD CHOICES [REDACTED VERSION]

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**Drug Therapy and Pregnancy:  
Unknown Risks Lead to Hard Choices**

*A Proposal to Improve the Quality of Information Available to Pregnant Patients in  
Selecting Treatment Options*

A Food and Drug Law Final Paper

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**Part I**

**The Effects of Drug Therapy on Pregnant Women:**

**A Personal Introduction**

[redacted]

**Part II**

**Pre-market Testing and the Exclusion of Fertile Women**

The questions of a pregnant woman on a drug like Cabergoline are hard if not impossible to answer. The problem is that the knowledge we have about drug effects on pregnant women (and in fact all fertile women) is limited. Women capable of becoming pregnant have traditionally been excluded from participating in pre-market testing studies. Women have been barred from acting as subjects in clinical trials, both de jure (explicit exclusion criteria in the protocol) and de facto (“inadvertent” failure to recruit women or to conduct the trial in a manner that realistically permits women to participate).<sup>1</sup> As recently as 1977, the FDA issued guidelines containing a policy to exclude women of childbearing potential from clinical trials. Such women were broadly defined to include essentially all pre-menopausal women not surgically sterilized.<sup>2</sup>

The old logic justified gender-based exclusion by positing that men were typical of all humans and could therefore constitute a complete subject population in drug trials. The thinking was that if an aspirin a day would prevent heart attacks in men, it would surely do so in women.<sup>3</sup> However as we have learned over time, such is not the case with all drugs. It has been demonstrated repeatedly that both female menstrual cycles and exogenous estrogens used in contraceptives and hormone replacement therapy can dramatically affect the utilization of a wide range of drugs including diazepam, insulin, tetracylin, rifampin and anti-convulsants.<sup>4</sup> Therefore, monitoring the safety and effectiveness of a particular drug on male subjects has limited use as applied to non-male subjects. Extrapolating from men to women regarding drug reactions is extremely difficult. Extrapolating from men to *pregnant* women is near impossible.

During pregnancy, maternal physiological changes occur which are relevant to drug distribution, metabolism and elimination. It has been demonstrated that pregnant women experience a plasma volume expansion and a corresponding increase in cardiac output. There are also changes in regional blood flow. One of the

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<sup>1</sup>Merton, Vanessa. The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (A.K.A. Women) From Biomedical Research. *The Texas Journal of Women and the Law*. 1994. 310-11.

<sup>2</sup>Charo Alta R., Protecting Us to Death: Women, Pregnancy and Clinical Research Trials. *St. Louis University Law Journal*. 1993. 139-140.

<sup>3</sup>Charo 141.

<sup>4</sup>Merton 322.

most pharmacokinetically important changes that pregnant women undergo is the decrease in serum albumin. Because drugs bind to serum albumin, a decrease in the concentration of this substance in the pregnant woman's body may lead to an increase in the apparent distribution volume and elimination clearance of many drugs.<sup>5</sup> The therapeutic significance of these changes is well demonstrated by the administration of Theophylline, a broncho-dilator commonly used to treat the asthma that accompanies about one in twenty five pregnancies.<sup>6</sup> Because of the changes in albumin concentration during pregnancy, the therapeutic dose range of Theophylline is reduced by approximately fifty percent for pregnant women in order to avoid the nausea, vomiting, and tremulousness that could accompany the dosages developed for non-pregnant persons, as well as to avoid having superfluous dosages cross the placenta and transfer to the fetus.<sup>7</sup> ACE inhibitors are another class of drugs that have been found to interact differently in the bodies of pregnant women. In 1992, the FDA had to prohibit the use of ACE inhibitors for pregnant women when it was discovered belatedly that these drugs caused serious renal complications and even death to newborns.<sup>8</sup> One could conclude that no drugs should be used in pregnancy, so as to avoid any potential problems. On the other hand, if agents such as ACE inhibitors are truly effective, why should pregnant hypertensive women be denied access to them?

Because pregnant women are physiologically different than other individuals and these differences affect drug absorption, distribution, and clearance in some known and many unknown ways, the exclusion of pregnant women from clinical trials is particularly troublesome. First of all, doctors and their pregnant patients have little to guide them in making decisions about which drugs are appropriate to optimize the health and well being of the mother and her fetus during the gestational period. Further, many mothers who wish to par-

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<sup>5</sup>Charo 159.

<sup>6</sup>Left unmanaged, asthma increases the risk of premature birth, perinatal mortality, low birth-weight, and pre-eclampsia. Thus, in addition to its usual risk to women's health, it adds special risk for both the fetus and mother during pregnancy and delivery

<sup>7</sup>Charo 159.

<sup>8</sup>Postmarketing Surveillance for Angiotensin-Converting Enzyme Inhibitor Use During the First Trimester of Pregnancy – United States, Canada, and Israel, 1987-1995. JAMA. 1997; 277 n15 p1193(2).

ticipate in experimental studies in order to receive basic healthcare (an increasingly common phenomenon) are not able to do so.<sup>9</sup> Lastly, exclusion from clinical trials means that pregnant women become guinea pigs once a new therapy hits the marketplace. Women who need to continue drug therapies during pregnancy for a variety of reasons are forced to “test out” the new drugs for the first time themselves.

By excluding fertile women from participating in clinical trials, we discount the important interest society has in protecting women against disease and adopt a framework that models efforts towards disease prevention upon a hypothetical male patient. The problem exists in numerous fields. In tort law, the “reasonable man” standard is indeed based upon a masculine persona and includes all the protective and aggressive instincts of a man. In cases of battery, the “reasonable man” has traditionally had a man’s judgment about what is offensive. In negligence, the “reasonable man” traditionally has had a man’s conception of emotional distress, and a man’s expectation for resulting compensation. Although legal standards rest on a man’s perception of justice in many important areas, this male-centric tendency is particularly damaging in the context of healthcare – where ignoring the unique concerns of women can result in a host of medical inequalities that affect quality and length of life. At issue is the appropriateness of extrapolating health risk data from men to women, the priority women’s health issues receive from the medical research community, and the lack of knowledge we have about women’s health due to the historical exclusion of women in clinical research.

As to the last of these, the National Institute of Health (NIH), which sponsors billions of dollars in medical research each year, has made research on women’s health a new priority by undertaking a fourteen-year, \$625 million Women’s Health Initiative, establishing an Office of Research on Women’s Health, and requiring that women be included in most NIH-funded studies.<sup>10</sup> Other research organizations, recognizing the lack of available information on women’s health, also have begun to sponsor major studies that focus specifically on women’s health issues, such as breast cancer and ovarian cancer. In keeping with this spirit of inclusion,

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<sup>9</sup>Merton 320.

<sup>10</sup>Charo 136.

FDA policy now aims at enhancing the participation of women in clinical trials.

However, pregnant women will still be the subject of extensive exclusions<sup>11</sup>, perpetuating a situation in which pregnant women fear taking even the most seemingly innocuous of drugs for fear of fetal damage. Drug companies fear liability for potential injuries to the offspring of pregnant women. Nervousness stems from the fact that an unborn child could bring suit as a result of birth defects.<sup>12</sup> Typically parents cannot waive causes of action on behalf of their children, and virtually all jurisdictions allow tort claims for prenatal injuries provided the child is born alive.

Although the inclusion of pregnant women in clinical trials may result in serious fetal injury, it is my contention that the exclusion of pregnant women from clinical trials has just as many or more harmful effects as inclusion and simply transfers liability from the drug company to the prescribing doctor. Without pre-market testing on pregnant subjects, it is difficult to predict in advance what the results of drug administration on pregnant women will be. Although the drugs are labeled with a Pregnancy rating of A, B, C, D, or X according to how dangerous the medication is suspected to be for pregnant women, there is a lot of guess-work inherent in this designation. Given the exclusion of pregnant women at clinical drug trials and the small number of inadvertent human exposures during the clinical trials, most medications (66%) are assigned to pregnancy category C, which indicates that human data for the drug are lacking and animal studies were positive or are not done. Less than 1% of medications have the Pregnancy Category “A” rating because very few drugs have actually been studied extensively in pregnant women in a well-controlled manner.<sup>13</sup>

The irony of the situation is evident: because researchers are so skittish about the risk of fetal harm, they bar women who might be pregnant – which to them includes every fertile female – from their research. But

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<sup>11</sup>Charo 137.

<sup>12</sup>Observations and reports of birth defects in children and women who had been treated with Thalidomide or Benedictin brought liability concerns to the forefront. See Mastorianni, Anna C. HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons From DES. *Duke Journal of Gender and Law Policy*. 1998 168-69.

<sup>13</sup>Weiss, Sheila R., PhD. Prescription Medication Use in Pregnancy. *Medscape Pharmacotherapy*. 2000. Available at: <http://www.medscape.com/medscape/pharmacology/journal/2000/v02.n06/mp7387.weis/mp7387.weis.html>

when it comes time to prescribe, market, and profit from drugs, drug companies do not bar women, including women of childbearing capacity. Due to risk-averseness on the part of the drug company, we encounter a situation in which doctors must (1) use anecdotal, uncontrolled evidence to decide whether a pregnant patient is better off with or without drug therapy and (2) carry extensive potential liability for injury to the drug-consuming patient. While the drug company is at liberty to use a simple disclaimer to avoid liability,<sup>14</sup> the doctor is left on the line with little information to make the tough decisions. If the doctor does prescribe the drug believing that the benefits outweigh the costs and he or she is wrong, it is the doctor and not the drug company that will be liable for advising the patient to undertake an “off-label” use of the drug.

And where is the FDA in all this? Well, despite the fact that the FDA has approved the drug and has determined that the benefits outweigh the costs, it has only done so with respect to the population at large. Yet, the FDA approved drug can be used by EVERY member of the population – despite the fact that the risk benefit distribution has not been analyzed across the population of drug-using patients. “Exactly who sustains the most risk?” is a question that the FDA does not ask. We as the drug-consuming public expect that using an FDA approved drug may entail some degree of risk. A product may be deemed safe even though it has risks as long as such risks are outweighed by the magnitude of the benefit expected and the alternatives available.<sup>15</sup> But we generally assume that the risk is spread across the population. We do not expect that with respect to a particular drug product, the vast majority of the risk of administration of the product will be concentrated on a highly selective subsection, such as pregnant women.

Granted the FDA requires that consumers be warned of the lack of knowledge about a drug’s effects in pregnant women, but this warning is not enough. Once medical products are on the market, ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products

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<sup>14</sup>Merton 336.

<sup>15</sup>Phillips, Jerry. FDA Efforts at Minimizing the Risks of Preventable Adverse Drug Events. Medscape Pharmacists. 2000. Available at: <http://www.medscape.com/Medscape/pharmacists/journal/2000/v01.n04/mph7174.phd/mph7174.phd.01.html>

wisely, thereby minimizing adverse events. But, drug administration is often a necessity of maintaining good health. And, despite the absence of adequate studies of the safety and effectiveness of prescription drugs for pregnant women, physicians prescribe, and pregnant women take, a surprisingly large number of drugs. According to a 1997 National Ambulatory Care Survey by the National Center for Health Statistics, 38% of pregnant women are prescribed medications at office visits.<sup>16</sup> Physicians reported prescribing three or more medications to their pregnant patients at 1.1 million office visits.<sup>17</sup>

Without systematic research on the effects of drugs in pregnant women, physicians and their pregnant patients are engaging in a kind of Russian roulette, courting the “random disaster... of inadequately investigated drugs.”<sup>18</sup> The patient risks the unknown health consequences of the drug, not just to her body but also to her offspring; the physician risks legal consequences if the adequacy of warnings to the patient comes into question. Many pregnant women are taking drugs without any real basis for predicting their effects. Meanwhile other pregnant women are unnecessarily deterred from taking a drug they need for fear of those untested effects. This may have serious implications for women’s health and the ultimate health of this nation’s children.

### **Part III**

#### **An Exception To a General Policy of Exclusion:**

The FDA does make some exceptions to the general rule excluding pregnant women from pre-market testing in cases – particularly where the woman is confronted with a life threatening disease with no effective

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<sup>16</sup>National Center for Health Statistics, CDC. 1997 National Medical Care Survey (public use data files). Available at: <http://www.cdc.gov/nchs/dataawh/ftpserve/ftpdata/ftpdata.htm>

<sup>17</sup>Weiss “Internet page” 1.

<sup>18</sup>Merton 327-28.



alternative treatment.<sup>19</sup> After much ado, pregnant women with AIDS were included in the pre-market clinical trials for AZT.<sup>20</sup> For a woman with AIDS or another such terminal disease, access to early clinical trials may be the only treatment available. And in such cases, some risk to the fetus is tolerated in the hopes that the drug trials will be “therapeutic” for the pregnant woman. But the regulations do not clearly specify the degree of health benefit necessary to call an experimental treatment “therapeutic” for the pregnant woman. This has led to some counterintuitive and perhaps irrational results:

A drug that relieves severe nausea is ordinarily [considered] therapeutic, as it provides for relief and helps maintain adequate appetite and nutrition. But if a woman is otherwise terminally ill, even significant symptomatic relief could be deemed ‘non-therapeutic’ for the pregnant woman because it will do nothing to alter her prognosis. Similar experimental therapies that offer a last, albeit slim, hope can be deemed non-therapeutic.<sup>21</sup>

Where research is deemed non-therapeutic for the mother, the regulations limit participation to cases where the “risk to the fetus is minimal.” This would effectively preclude a variety of basic studies designed to determine whether certain drugs cross the placenta or are metabolized in substantially different fashion in pregnant women, as animal studies may be insufficient to demonstrate a “minimal” risk to the fetus.

One important consideration here is that “risk to the fetus” may or may not manifest itself as risk to the future unborn child. A risk to the fetus that is not going to term is a risk that will never be experienced by a sentient being. Clearly until the moment of viability (when most states forbid all but therapeutic abortion), the fetus may be destroyed by abortion. It is hard to argue that a fetus that has been affected by a drug prior to its destruction by abortion is any more “harmed” than one destroyed by abortion when untouched by such substances. According to author R. Alta Charo, “a risk that a pre-viable fetus will be unable to go to term is not, in and of itself, a ‘harm’ if such fetus has no right nor desire to be born.”<sup>22</sup> A better

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<sup>19</sup>Charo 160.

<sup>20</sup>Mastoian 170.

<sup>22</sup>Charo 161.

formulation of the regulations, according to Charo would distinguish between research done on pregnant women who plan to go to term and those who do not.

However, this argument if taken to its logical end could result in disastrous practical consequences. Making distinctions based on subjective intent (here an intent to abort) is always difficult, and there is no need to set up a framework in which women in grave financial need could be coerced into using their bodies as test tubes and allowing experimentation followed by abortion of their unborn fetuses in exchange for money or free healthcare. It is my contention that the regulations should allow for experimentation on pregnant women where (1) the disease in question is life-threatening and there are no other viable alternatives or (2) where risk to the fetus is demonstrated to be “minimal.” These conditions should have to be satisfied without reference to the intent on the part of the mother to carry the pregnancy to term. Notably, this rule would still exclude pregnant women from participating in most pre-market drug studies. There seems to be too much potential for harm to the subjects tested to justify large-scale inclusion of pregnant women in drug trials for those who do not absolutely need the drug therapy for life and who are simply being used as data points in an effort to benefit future drug-consumers. In order to protect pregnant women and their fetuses at large, we must therefore turn to another method of scientific inquiry.

## **Part IV**

### **Post-Marketing Surveillance as a Tool for Determining the Safety and Effectiveness of Drugs Used by Pregnant Women**

Since pregnant women are by and large excluded from pre-market pharmaceutical studies, in many cases post-market monitoring of patients’ actual experiences with the drug remains the only practicable way for

the public to learn about the consequences of drug use by pregnant women.<sup>23,24</sup> Yet, there is a surprising scarcity of epidemiological projects on adverse drug reactions (ADRs) and even of post-market drug usage data. Currently, the FDA maintains a system of postmarketing surveillance (i.e. the MedWatch program) in order to monitor suspected adverse drug reactions (ADRs)<sup>25</sup> associated with the use of approved medical products. In this way, the FDA hopes to identify adverse events that were not caught during drug development and pre-marketing review.<sup>26</sup> However, for reasons that will be discussed below, the FDA's current system of post-marketing surveillance is inadequate and must be amended to provide clear guidance and incentives for patients, drug companies, and health care providers to work together in a systematic effort to disseminate needed risk management information.

Currently, most of the information we receive about a drug's post-market effects in the population comes via spontaneous reports. However, by their very nature, "spontaneous" reports tend to be unorganized, sporadic, and lacking in useful detail. Further, the information contained in such reports is rarely collected and given to a centralized authority for systematic inspection and analysis. Because of the development of national ADR reporting systems and concomitant regulations and guidelines, patients and doctors are often at a loss as to whom to report suspected ADRs to – the government, the pharmaceutical company etc.... In practice, direct reports to manufacturers account today in the Western world only about fifty percent of the accessible reports. Forty percent are addressed to national authorities and with only limited access to

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<sup>23</sup>It was via the formation of the ACEI Registry by the Organization of Teratology Information Services (OTIS) that we learned that use of certain FDA approved anti-hypertensive drugs, angiotensin-converting enzyme inhibitors (ACEIs), in the second and third trimesters of pregnancy causes renal tubular dysplasia, hypocalvaria, intrauterine growth retardation, and patent ductus arteriosus in the fetuses of exposed women. Postmarketing Surveillance for Angiotensin-Converting Enzyme Inhibitor Use During the First Trimester of Pregnancy – United States, Canada, and Israel, 1987-1995. JAMA. 1997; 277 n15 p1193(2).

<sup>24</sup>The teratogenic effects of thalidomide and more recently, accutane, were also identified via post-market surveillance. Weiss "Internet Page" 2.

<sup>25</sup>The American Society of Health-System Pharmacists (ASHP) defines an ADR as any unexpected, unintended, undesired, or excessive response to a medicine that (1) requires discontinuing the medicine (2) requires changing the medication therapy (3) requires modifying the dose (4) necessitates admission to the hospital (5) prolongs stay in a health-care facility (6) necessitates supportive treatment (7) significantly complicates diagnosis (8) negatively affects prognosis or (9) results in temporary or permanent harm, disability, or death. Vitillo, Josephine A. Adverse Drug Reaction Surveillance: Practical Methods for Developing a Successful Monitoring Program. Medscape Pharmacists, 2000. Available at: <http://www.medscape.com/Medscape/pharmacists/journal/2000/v01.n06/ MPH7421.viti/MPH7421/viti.01.html>

<sup>26</sup>The Agency uses this information to initiate labeling updates and, on rare occasions, to reevaluate the marketing decision.

the manufacturer. Sometime even information on age and sex is not provided. Only about ten percent of the ADR case reports are published. Thus the medical community and the public are only receiving a small proportion of the valuable information available about the post-market effects of drugs in portions of the population left unstudied by pre-market trials.

Further, although spontaneous reports provide early signals, they (1) cannot quantify a risk and (2) need validation. Spontaneous reports in their current form do not reliably detect adverse drug reactions that occur widely separated in time from the original use of the drug or that represent an increased risk of an adverse event that occurs commonly in populations not exposed to the drug.<sup>27</sup> In announcing the MEDWATCH, a program which encouraged health care professionals to report serious events suspected to be caused by products regulated by the FDA, then commissioner Kessler wrote that the lack of spontaneous reports linking silicone breast implants with autoimmunelike disorders<sup>28</sup> delayed the detection of this problem even though implants had been in use for approximately 30 years<sup>29</sup> Identification of ADRs associated with long-term administration of drugs for chronic diseases also remains problematic. Additional limitations of spontaneous reporting include both erroneous reports and the fact that prescribing patterns and reporting rates are not linked.<sup>30</sup> Comparisons of physician reports of ADRs with expert reviewers' opinions or with standardized assessment methods have demonstrated poor agreement between physicians and the other methods in as-signing causality of the ADR to the medication.<sup>31</sup> Likewise, the quality of patient reports is dubious. In a study that relied on reporting forms and telephone questioning, patients were less likely to attribute "events"

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<sup>27</sup>Brewer T, Colditz GA. Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs. *JAMA*. 1999; 281 i9 p824(1).

<sup>28</sup>Autoimmunelike symptoms are relatively common in women without implants. The increase in risk exposure, if any, is likely to be small, and symptoms occur years after the initial exposure. Adverse drug reactions meeting this description are unlikely to be reliably detected by any spontaneous reporting system. Brewer "Internet Page" 3.

<sup>29</sup>Kessler, DA. Introducing MEDWATCH: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems. *JAMA*. 1983;249:2226-2228.

<sup>30</sup>In one study of almost 30,000 general practitioners in the United Kingdom, Inman and Pearce found that 10% of practitioners wrote approximately 40% of the prescriptions for recently released drugs. Furthermore, the more likely a physician was to prescribe a new drug, the less likely he or she was to submit an ADR report. Inman W, Pearce G. Prescriber Profile and Post-Marketing Surveillance. *Lancet*. 1993; 342:658-661.

<sup>31</sup>Miremont G, Haramburu F, Begaud B, Pere JC, Dangoumau J. Adverse Drug Reactions: Physicians' Opinion Versus a Causality Assessment Method. *European Journal of Clinical Pharmacology*. 1994;46:285-289.

to the prescribed medication than an expert panel that reviewed the event forms.<sup>32</sup>

Methods to evaluate ADRs using data from clinical trials, medical records, and computerized databases of medication users and nonusers must be developed to complement spontaneous reporting systems. Without these methods, potentially important ADRs will remain undetected, and spurious associations between adverse outcomes and medications and devices will remain unchallenged. The creation of computerized prescription and laboratory databases has greatly enhanced the ability of institutions and organizations to screen for known ADRs.<sup>33</sup> Changes in medication orders, orders for antidote medications such as antihistamines or opiate agonists, drug levels, and laboratory information such as *Clostridium difficile* toxin titers have all been used as screens.<sup>34</sup> Screening adverse event monitors has been more effective in documenting ADRs than simplified voluntary reporting or educational programs. Hospital-based systems can greatly increase the reporting of known ADRs, but their value for identifying new, unknown ADRs remains unclear. Only ADRs that occur during hospitalization are recognized. Many hospital systems do not have sufficient sample size to reasonably detect unknown ADRs. Further, ADRs that occur after discontinuation of the offending medication may be missed by these systems. Since these systems rely on algorithms to detect ADRs, events unrelated to the algorithms go unnoticed.

*An effort by the drug companies themselves to encourage exploration of the effects of their products on pregnant subjects in post-market studies would be most helpful in the effort to provide for the health of pregnant women. Unlike hospitals, which only have access to their own patients, drug companies have access to the broadest population of individuals who use their products. The question is simply how to create an incentive for drug companies to*

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<sup>32</sup>Mitchell, AS, Henry DA, Sanson-Fisher IL, O'Connell DL. Patients as a Direct Source of Information on Adverse Drug Reactions. *BMJ*. 1988;297:891-893.

<sup>33</sup>Vitillo "Internet Page" 7.

<sup>34</sup>Brewer "Internet Page" 4.

*increase post-market study of pregnant women when they are already easily shielded by a lack of information and a label.*

## **Part V**

### A PROPOSAL FOR IMPROVING THE QUALITY OF AVAILABLE INFORMATION ON DRUG EFFECTS IN PREGNANT POPULATIONS

The FDA should deliver extended grants of exclusivity to those drug companies that publish the findings of post-marketing surveillance studies in pregnant women. Under this system, the drug company would be able to benefit economically by dominating the market for the drug for an entire year. In return, doctors and patients would benefit from the increased information flow. In order to take advantage of this quid pro quo, the drug company would have to produce a statistical analysis of a population of pregnant women of sufficient size. Although the collection of spontaneous reports alone would not be sufficient to qualify the drug company for a lengthened term of exclusivity, the drug company *would* be required to make spontaneous reporting easy. Drug companies would be required to set up hot lines, fax lines, and email addresses for the sole purpose of collecting healthcare provider and patient ADR reports. All drug products would need to display a noticeable label containing instructions on how patients should contact the drug company in case of an ADR. Finally, the FDA would receive all such reports from the drug companies and use such information in conjunction with results from pre-market clinical trials in order to make decisions about whether to revoke approval or provide strong cautions to doctors or pregnant women in the literature or on the drug label.

In addition to publishing case studies that spring from spontaneous reports, the drug companies would also have to *affirmatively* track women taking their drug and seek their consent to conduct examinations and interviews and review medical records. Because pregnant women are not initially included in clinical trials, it is important that those who must take drug therapies are identified and recruited (before the outcome is

known) and then followed until the end of pregnancy. Volunteerism among pregnant women is an important prerequisite to making the system work. And because so many women already use drug therapies during pregnancy, finding willing subjects should not be a major obstacle. Perhaps drug companies could encourage patients to disclose health information by providing the drugs or the concomitant health care consultations free of charge. By seeking out a random sample of pregnant women to follow on the course of their drug use in a post-market study, we will strive to recreate as closely as possible the conditions that produce useful information in pre-market clinical trials. In this way we will be able to add a level of scientific validity to the post-marketing surveillance system that does not currently exist with the spontaneous reporting procedure. In order to make the information obtained useful, after compiling the data, the drug company would record the results of their post-market analysis on a portion of the FDA web site so that the necessary information would be accessible to doctors and patients alike.

Currently drug companies do not have the proper incentives to seek out more knowledge about the effects of their products in pregnant populations. For example, there is no registry set up to collect information on the effects of Cabergoline on pregnant women. When contacted for information on the effects of Cabergoline in pregnant women, the manufacturer of the drug, Pharmacia and Upjohn, simply mailed out a summary of data on pregnant women who *inadvertently* took the drug while pregnant during the *pre-approval* process.<sup>35</sup> That the sample size and purported effects were statistically insignificant did not incite the company to follow up with added research on pregnant women post-market. The fact that many women desperately need such a drug to ovulate and become pregnant in the first place also apparently did not act as a motivating factor in encouraging further research in pregnant populations.

While sad, this state of affairs is relatively unsurprising. The fact is that drug companies are primarily concerned about the bottom line. They want to sell their products to as many customers as possible and

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<sup>35</sup>Pharmacia and Upjohn, fax to Lori Goldstein, 22 January 2001.

avoid liability. In the case of pregnant women, drug companies are able to use disclaimers to transfer tort liability to the prescribing doctor and have little interest in ensuring that the doctor's advice about drug use is well-informed. Once the drug company has FDA approval, it is in a sense "home-free." One solution to this inequity would be to try to stick it to the drug companies in the form of liability – in essence to shift the blame for harm to pregnant women back to the producer of the drug. However, such a step might hamper drug development at large and would certainly lead to delays in the pre-market approval process. Giving the drug company a positive incentive to learn more about the effects of its products in pregnant women after FDA approval is a much better alternative. Here we encourage the drug company to profit and in fact give it an extended patent on its drug products in exchange for consumer data regarding the safety and effectiveness of these products in pregnant women. Although the grant of a one-year monopoly would likely produce an increase in the initial cost of the drug in its first year on the market, this is a small price to pay for the added health benefits associated with the protection of pregnant women and their offspring. Further, by focusing our efforts on increasing the quality of postmarketing surveillance rather than pre-market testing, we avoid further delays in the pre-approval process, encourage drug companies to invest in development and research and provide a set of rules by which drug companies would be foolish not to invest their resources in providing healthcare providers with the information necessary to inform and advise their pregnant patients. Only in such a situation, where the healthcare providers are informed about the risks and benefits of the drug in question to the populations they serve, can they reasonably be expected to shoulder the liability for adverse consequences.

By providing drug companies with extended grants of exclusivity, the FDA has the ability to empower pregnant women to take control of their health and make informed decisions. Granted post-marketing surveillance will always catch ADRs at a later stage of the game than pre-market clinical trials, but in the case of pregnant women – where we must concern ourselves with potential harms to a future sentient child



- increased rigor in the method and quantity of post marketing surveillance techniques seems like the only way to go. Pregnant women should be able to learn from the experiences of other pregnant women. That drug companies can and should take an affirmative step in collecting and disseminating information about the use of their products by pregnant populations is a no-brainer. The drug companies will not, however, act unprovoked; FDA needs to take the first step and create an incentive for the drug companies to take action on behalf of pregnant women and children.